# REMARKS

## Present Status of the Application

The Office Action dated November 07, 2008 objected the specification for containing sequence disclosures as set for in 37 C.F.R. 1.821(a)(1) and (a)(2). Claims 19-25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 19-25 were rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. Claims 19-25 were rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al. (WO 03/000656 A2).

Claims 19 and 21-25 have been amended for clarification purposes or correcting informalities. The specification has been amended for incorporating SEQ ID NOs for clarification purposes and complying with the nucleotide sequence disclosure requirements. It is believed that the amendments are supported by the original specification and drawings of this application and can overcome the objections. After entering the amendments and considering the following discussions, a notice of allowance is respectfully solicited.

## Discussion for the objections

The specification was objected for containing sequence disclosures as set for in 37 C.F.R. 1.821(a)(1) and (a)(2).

The specification has been amended by assigning SEQ ID NOs. to the sequences recited in page 17, 1st paragraph and page 36, 2nd paragraph of the specification of the present application.

However, the sequences recited in page 13 of the specification of the present application simply are variants of SEQ ID NO: 3. This means that sequence SEQ ID NO: 3. is the core sequence and therefore the most important sequence of all the possible variants. The partial sequences X and Z have the meaning of chemical residues. They do not present independent sequences and are therefore regarded as no need for their own SEQ ID NOs.

Entry of the amendments to the specification is respectfully requested.

Withdrawal of these objections is earnestly requested.

**Discussion of 101 and 112 rejections**

Claims 19-25 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Especially, the term "TGF-RII" is not clearly defined and no steps are involved in the method/process claims.

Claims 19-25 were rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process.

Claims 19 and 21-25 have been amended to replace the abbreviation TGF-RII with "Transforming growth factor β receptor II" in claims 19, 21 to 25 and the abbreviation TGF-β with "Transforming growth factor β" in claim 24.

Moreover, claim 19 has been amended as "Use of at least one oligonucleotide ..... which comprises administering a therapeutically or prophylactically effective amount of said oligonucleotide having said sequence, mimetics, variants, salts or optical isomers of said

sequence to a mammal for promoting...", so that steps involved in the "Use" claims are clearly recited. Claims 23 and 25 have been amended for clarification.

Withdrawal and reconsideration of these 112 rejections are respectfully requested.

**Discussion of Rejections under 35 U.S.C 102**

Claims 19-25 were rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al. (WO 03/000656 A2; hereinafter Murray).

Claims 19 and 21-25 have been amended to provide more descriptions for clarification purposes and for correcting informalities.

Amended claim 19 partially recites:

*19.* ***Use of at least one oligonucleotide having a sequence at least 80% identical to a sub-sequence of SEQ ID NO 1*** *comprising 8 to 50 nucleobases, wherein said sequence is capable of hybridizing sufficiently with the region encompassing the translation initiation or termination codon of the open reading frame of the gene encoding Transforming growth factor β receptor II, or a region of the mRNA encoding Transforming growth factor β receptor II ……* ***which comprises administering a*** *therapeutically or prophylactically* ***effective amount of said oligonucleotide*** *having said sequence, mimetics, variants, salts or optical isomers of said sequence* ***to a mammal for promoting successful regeneration and functional reconnection of damaged neural pathways.***

(Emphasis added)

Murray (WO 03000656 A2) merely teaches TGF-βRII antisense oligonucleotides for treatment of diseases that are associated with TGF-βRII expression. Murray focuses on the treatments of cancerous diseases and the diseases related to the activation of the immune system.

According to the present application, the claimed "Use" of antisense oligonucleotides is directed to promote regeneration and functional reconnection of damaged neural pathways. That means the antisense oligonucleotides of the present application are utilized to prevent and treat disorders of the central nervous system (CNS) and neuronal stem cell renewal.

Examples 6, 7 and 8 and the corresponding Figures 6, 7 and 8 of the present application show that the oligonucleotides as recited in claim 19 effect the activity in central nervous system cells. In detail the effect of the oligonucleotides on the TGF-β1 induced inhibition of neural stem and precursor cell proliferation was investigated. Example 6 worked with cultured neural stem and precursor cells while Examples 7 and 8 applied the antisense oligonucleotides to the brains of living animals. Example 6 shows that the induced inhibition of neural stem and precursor cell proliferation in cell culture was completely and specifically blocked by the antisense oligonucleotide treatment (figure 6). Examples 7 and 8 demonstrate that administration of the antisense oligonucleotides successfully prevents and treats the induced inhibition of neural stem and precursor cell proliferation in living animals. Thus, the oligonucleotides as recited in claim 19 of the present application have been shown to have a surprising advantageous effect of activity in central nervous system cells.

Nowhere in Murray's teachings teaches or suggests that its TGF-βRII antisense oligonucleotides might be useful in treatment of neuronal disorders. To one ordinary artisan in

this field, such usage or effects would not be anticipated or expected based on the disclosures of Murray.

Even considering Murray's statement "Mutant function or overactivity of TGF-β signaling components is implicated in cancers of the colon, esophagus, pancreas, lung, and breast, as well as in hyperproliferative disorders of the kidney, atherosclerosis, and rheumatoid arthritis (Imai et al., J. Nephrol., 1998,11,16-19; Markowitz, J. Clin. Invest., 1997,100,2143-2145; Pasche, J. Cell Physio., 2001, 186, 153-168 ; Piek et al., Faseb J., 1999,13, 2105-2124)." (page 1, lst paragraph) as related arts, Murray just mentions possible associations of TGF-β signaling components and certain diseases.

Furthermore, the Examples of the present application show that the claimed oligonucleotides have a real curative effect on neural cells in cell culture as well as in an animal model.

In contrast to the Examples of the present application, Murray only shows that its antisense oligonucleotides affect the expression of TGF-βRII in different human cell lines and mouse cells in cell culture. Murray does not show that the effect of the antisense oligonucleotides to reduce expression of TGF-βRII is connected to a real curative effect. In the case of the used cancer cell lines of human transitional cell bladder carcinoma or human lung carcinoma or human hepatoblastoma cells, a desired curative effect could have been a decreased proliferation of cancer cells. However, Murray does not show an effect like this. Thus the curative effect on neural cells in cell culture as well as in an animal model of the antisense oligonucleotides of the present application would not be expected based on the disclosure of Murray.

While the present application relates to use of at least one oligonucleotide for supporting regeneration of damaged nerves and for treatment of diseases associated with damaged nerves, Murray exclusively deals with cancer treatment and does not even suggest any connection between regeneration of nerves and TGF-βRII. In fact, to any artisan in this field, Murray's disclosures go into a very different direction other than that of the present invention.

Moreover, even if considering that Murray had shown a curative effect like decreased proliferation of cancer cells, it would have led a person skilled in the art to conceive that Murray's oligonucleotides have a destructive effect on cancer cells.

However, in the present application, the curative effect consists in an increase of proliferation of cells, namely neural stem and precursor cells.

Clearly, Murray's disclosures not only fail to teach or suggest the "Use" of antisense oligonucleotides for promoting regeneration and functional reconnection of damaged neural pathways as claimed in the present application, but also fail to enlighten one ordinary artisan with the curative effect on neural cells in cell culture as well as in an animal model of the antisense oligonucleotides of the present application.

Accordingly, as discussed above, Murray fails to disclose each and every feature as recited in independent claim 19, and independent claim 19 patently defines over the reference Murray. Claims 20-25 depending from claim 19 therefore are not anticipated by Murray for the reasons noted above, as well as for the additional features recited therein.

Reconsideration and withdrawal of above 102 rejections are respectfully requested.

## CONCLUSION

For at least the foregoing reasons, it is believed that the pending claims of the present application patently defines over the prior art and are in proper condition for allowance. If the Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

Respectfully submitted,
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